ZINC FINGER NUCLEASE-BASED STEM CELL THERAPY FOR AIDS

Grant Award Details

ZINC FINGER NUCLEASE-BASED STEM CELL THERAPY FOR AIDS

Grant Type: Disease Team Research I

Grant Number: DR1-01490

Project Objective: Goal of the project is develop Zinc finger nuclease based stem cell gene therapy for AIDS .

Investigator:

Name: John Zaia
Institution: City of Hope, Beckman Research Institute
Type: PI

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Name: David DiGiusto
Institution: City of Hope, Beckman Research Institute
Type: Co-PI

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Name: Paula Cannon
Institution: University of Southern California
Type: Co-PI

Disease Focus: HIV/AIDS, Immune Disease

Human Stem Cell Use: Adult Stem Cell

Cell Line Generation: Adult Stem Cell

Award Value: $14,536,969

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: Year 4 + NCE

View Report

Grant Application Details

Application Title: ZIinc Finger Nuclease-Based Stem Cell Therapy for AIDS

Public Abstract: Some years ago it was discovered that patients homozygous for a natural mutation (the Δ32 mutation) in the CCR5 gene are generally resistant to HIV infection by blocking virus entry to a cell. Building on this observation, a study published in 2009 reported a potential "cure" in an AIDS patient with leukemia after receiving a bone marrow transplant from a donor with this Δ32 CCR5 mutation. This approach transferred the hematopoietic stem cells (HSC) residing in the bone marrow from the Δ32 donor, and provided a self-renewable and lifelong source of HIV-resistant immune cells. After transplantation, this patient was able to discontinue all anti-HIV drug treatment, the CD4 count increased, and the viral load dropped to undetectable levels, demonstrating an effective transplantation of protection from HIV and suggesting that this approach could have broad clinical utility. But donors with the Δ32 CCR5 mutation are not generally available, and so how could we engineer an analogous CCR5 negative state in human HSC needed for bone marrow transplantation? A potential answer comes from zinc finger nucleases (ZFNs) which have been demonstrated to efficiently block the activity of a gene by cleaving the human genome at a predetermined site and altering the genetic sequence via an error-prone DNA repair process. This modification of the cellular DNA is permanent and can fully block gene function. Recently, ZFNs have been shown to inactivate CCR5 in primary human CD4 T cells, allowing them to preferentially survive and expand in the presence of HIV. A human clinical trial evaluating this approach is on-going, in which patient T cells are re-infused after ZFN-treatment to block CCR5 expression and possibly provide an HIV-resistant reservoir of CD4 T cells. The CIRM Disease Team proposes an approach to modify a patient's own HSC to circumvent the need to find matched donors that carry the Δ32 CCR5 mutation and yet provide a renewable and long-lasting source of HIV-resistant cells. Testing of this concept is proposed in selected AIDS lymphoma patients who routinely undergo HSC transplantation. Preliminary results in mice transplanted with ZFN-treated HSC show that ZFN-modified, CCR5-negative HSC are functional and support the reconstitution of the immune system. Importantly, after HIV infection, these mice have results similar to those observed in the human patient: (i) reduced viral loads, (ii) maintenance of CD4 T cells in peripheral tissues; and (iii) a powerful selective advantage for the CCR5 negative immune cells. These data support the development of a ZFN approach to treat AIDS patients by first isolating their HSC, modifying them using CCR5-specific ZFNs, and re-infusing them to reconstitute the immune system with CCR5-negative, HIV-resistant immune cells.

Statement of Benefit to California:	California has ~14% of all cases of AIDS in the U.S., and this translates into a medical and fiscal burden larger than any other state except NY. Antiviral chemotherapy accounts for approximately 85% of AIDS-related medical costs, and federal and state law requires that in California the AIDS Drug Assistance Program (ADAP) be the payer of last resort for these medications. In fiscal year 2007-08, the California AIDS Drug Assistance Program (ADAP) served 32,842 clients and filled over 953,000 prescriptions for these clients. The Governor's current spending plan (2009-09 Budget Act) called for $418M to support this program, with funds from several sources including federal (Ryan White Care Act), from an ADAP Rebate Fund, and from the California State General Fund. The ADAP Rebate Fund consists of monies paid to the state by the manufacturers of the drugs provided to the HIV/AIDS clients under the program. The ADAP budget has grown by ~15% yearly for several years, and based on an Legislative Analyst's Office (LAO) review, the problem faced is that, as the case load is increasing, support from the Rebate Fund is decreasing. It is projected by LAO that from a level of $80.3 million at end 2007-08, the Fund will decrease to $24M by 2009-10. The General Fund currently provides $96.3M to the ADAP budget, and it is projected that as the ADAP Rebate Fund shrinks, the shortfall will have to be met by increases from the General Fund by 2011-12. The alternative, as noted by LOA, is to implement cost-cutting measures that would likely increase the barriers to receiving care for some patients, impacting the health of some HIV/AIDS patients and increasing the associated public health risks. The basic problem is that HIV/AIDS is a life-long infection and our current strategy of treatment requires that medication be taken daily for a lifetime. Thus, there is a real need to develop a strategy of treatment that has the potential to reduce the duration of antiviral chemotherapy. This will have significant impact on the quality of life for persons with HIV/AIDS. In this proposal, a cellular therapy derived from genetically modified blood stem cells will be developed and preclinical studies completed, leading to its first evaluation in patients. As important is the benefit that the first test of this technology will have on the overall field of embryonic stem cell research. The ZFN technology used here will have application to other diseases and hurdles surmounted now will benefit future embryonic cell research.